

An Overview of Fracture Healing: Biological Basis, Modifying Factors, and Outcomes

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ABSTRACT

Among the most common musculoskeletal injuries worldwide, fractures contribute substantially to morbidity, disability, and healthcare expenditure across all age groups. Fracture healing is a unique regenerative process that restores the structural and functional integrity of bone through a precisely coordinated sequence of biological and mechanical events. Despite advances in surgical techniques and fixation methods, a significant proportion of fractures progress to delayed union or nonunion, underscoring the need for a comprehensive understanding of the mechanisms governing bone regeneration. This review provides an updated overview of the biology of fracture healing, emphasizing the cellular, molecular, and biomechanical processes involved. The fundamental types of fracture healing, primary and secondary, and the classical stages including inflammatory, reparative, and remodeling phases are described. The roles of inflammatory mediators, mesenchymal stem cells, angiogenesis, growth factors, and mechanical stability are discussed, along with patient-related, fracture-related, and treatment-related factors influencing healing outcomes. These include age, nutritional status, smoking, systemic diseases, fracture pattern, vascularity, fixation technique, and pharmacological influences. The etiology and clinical implications of common complications such as delayed union, nonunion, infection, and implant failure are addressed. Current and emerging strategies to enhance fracture healing are reviewed, including pharmacological agents such as bone morphogenetic proteins and parathyroid hormone analogues, surgical techniques, bone grafts and substitutes, and adjunctive physical modalities like low-intensity pulsed ultrasound and electrical stimulation. Special considerations in pediatric fractures, osteoporotic fractures, and polytrauma patients are highlighted. Recent advances in stem cell therapy, tissue engineering, regenerative medicine, and personalized fracture care are explored as promising future directions. A thorough understanding of fracture healing biology and modifying factors is essential for identifying high-risk patients, preventing complications, optimizing treatment strategies, and ultimately improving clinical outcomes and quality of life. This knowledge supports evidence-based decision making, multidisciplinary collaboration, rational resource utilization, and consistent improvements in modern orthopedic trauma practice.

Keywords- Fracture healing; Bone regeneration; Delayed union and nonunion; Biological and mechanical factors; Orthopedic trauma

I. INTRODUCTION

With an estimated prevalence that ranks them among the top causes of disability across all age groups, fractures are one of the most frequent traumatic injuries

affecting the musculoskeletal system globally. These injuries range in severity from straightforward stress fractures to intricate open fractures involving significant soft tissue injury. While the majority of fractures in healthy people mend via well-coordinated biological and mechanical mechanisms, a sizable percentage have

difficulties such delayed union and nonunion, which provide significant clinical and financial challenges.^{[1][2]}

Among adult human tissues, fracture healing is distinct in that it can completely restore the original structural and functional integrity of bone through a regeneration process as opposed to merely leaving scars. Many of the ontogenetic processes observed during embryonic skeletal development are recapitulated in fracture repair, which involves a tightly controlled series of cellular proliferation, differentiation, matrix production, and remodeling.^[3] Despite this amazing ability, problems are nevertheless clinically significant. According to contemporary estimates, 5–15% of fractures do not mend normally even with the best care, which results in prolonged morbidity, disability, pain, restricted mobility, and a lower quality of life.^{[2][4]}

In contrast to nonunion, which is a more serious failure of healing and is typically defined as a fracture that shows no signs of progression toward union within a clinically acceptable timeframe (typically six to nine months), delayed union refers to healing that is slower than expected for a specific bone and patient profile.^{[1][4]} These issues not only directly affect patient function but also lead to higher healthcare utilization, longer rehabilitation times, and substantial financial expenses for both patients and healthcare systems.^[4]

Mechanical stability, systemic physiology, and local tissue variables interact intricately in the biological process of fracture healing. The development of a hematoma at the site of injury sets off a coordinated inflammatory response that attracts mesenchymal progenitor cells necessary for the future creation of calluses and ossification.^{[5][6]} Neovascularization, efficient cellular signaling, and a suitable mechanical environment are necessary for successful repair, underscoring the interaction of biological and mechanical elements in determining healing outcomes.^[7]

II. BIOLOGY OF FRACTURE HEALING

Bone's structural and functional integrity is restored through the dynamic, tightly controlled biological process of fracture healing. In contrast to soft tissue healing, bone repair is a regenerative process that requires the coordinated action of progenitor cells, growth hormones, inflammatory cells, and mechanical stimulation. This process, which is impacted by both systemic and local stimuli, is very similar to the formation of the embryonic skeleton.^[3]

2.1 Types of Fracture Healing

2.1.1 Primary (Direct) Fracture Healing

Absolute mechanical stability is necessary for primary fracture healing, and this is usually accomplished by stiff internal fixation like compression plating. There is little to no callus production and a small fracture gap (less than 0.1 mm) with this kind of healing. Osteonal cutting cones that cross the fracture line directly remodel

the bone to restore normal bone architecture.^[3] Precise anatomical reduction and an unbroken blood supply are crucial to this process. Direct healing is less common in ordinary clinical practice since it can be hampered by any interruption in vascularity or stability.

2.1.2 Secondary (Indirect) Fracture Healing

The most prevalent mechanism is secondary fracture healing, which happens when regulated micromotion at the fracture site is made possible by relative stability. Intramembranous and endochondral ossification are combined in this kind of healing, resulting in the creation of a visible callus. Because secondary healing is biologically resilient and can withstand slight instability, it can be used with flexible fixation techniques and conservative treatment.^[8]

2.2 Stages of Fracture Healing

Each of the overlapping but biologically separate stages of fracture healing is distinguished by certain cellular activity, molecular signaling pathways, and biomechanical requirements. These phases consist of the remodeling, reparative, and inflammatory phases. For full bone regeneration, each cycle must be completed successfully; any interruption at any stage could result in nonunion or delayed union.^{[9][10]}

2.2.1 Inflammatory Phase

After a fracture, the inflammatory phase starts right away and usually lasts for a few days. Hematomas, which act as a temporary extracellular matrix rich in fibrin, platelets, and inflammatory mediators, are created when blood vessels at the fracture site are disrupted. This hematoma offers a biological milieu that encourages cellular recruitment in addition to mechanical stability.^{[11][5]}

Neutrophils and macrophages, among other inflammatory cells, migrate into the fracture hematoma and release prostaglandins, interleukin-1 (IL-1), interleukin-6 (IL-6), and tumor necrosis factor- α (TNF- α). These mediators control angiogenesis, promote the recruitment of mesenchymal stem cells (MSCs), and start the molecular cascade necessary for tissue regeneration.^{[11][2]}

By facilitating the shift from inflammation to repair, macrophages perform a crucial regulatory role. Experimental research has shown that fracture healing is severely hampered by macrophage depletion or excessive suppression of inflammation, such as with long-term NSAID usage, highlighting the crucial function of this stage.^{[3][1]}

2.2.2 Reparative Phase

The healing process starts a few days after the damage and could go on for several weeks. Mesenchymal stem cells from the periosteum, bone marrow, and surrounding soft tissues multiply and develop into chondrocytes and osteoblasts during this phase. As a result, a soft fibrocartilaginous callus forms that bridges the fracture gap and stabilizes the fracture site.^{[3][12]}

While intramembranous ossification takes place at the periosteal surfaces, endochondral ossification

predominates within the fracture space. Type II collagen and proteoglycans are produced by chondrocytes in the callus, creating a cartilage template that is eventually replaced by mineralized woven bone. Growth factors include insulin-like growth factor (IGF), platelet-derived growth factor (PDGF), transforming growth factor- β (TGF- β), and bone morphogenetic proteins (BMP-2, BMP-7) strictly control this change.^{[2][13]}

One characteristic that distinguishes the reparative phase is angiogenesis. By encouraging neovascularization, vascular endothelial growth factor (VEGF) makes it easier for the growing callus to receive nutrients and oxygen. Research has demonstrated a substantial correlation between delayed union and nonunion and decreased angiogenesis, underscoring the connection of skeletal and vascular regeneration.^{[13][11]}

2.2.3 Remodeling Phase

The last and longest stage of fracture healing, known as the remodeling phase, can take months or even years. Through a process of linked osteoclastic resorption and osteoblastic bone production, mechanically weak woven bone gradually gives way to ordered lamellar bone throughout this phase. The original internal architecture, mechanical strength, and shape of the bone are all restored by this technique.^{[3][14]}

By directing bone adaptation in accordance with Wolff's law, mechanical loading plays a critical role during remodeling. Osteoblast activity is stimulated by functional stress, whereas bone resorption results from inactivity. Near-normal bone morphology is restored through the restoration of the medullary canal, normalization of cortical thickness, and resorption of excess callus.^{[1][3]}

Remodeling efficiency is greatly influenced by systemic factors like nutrition, metabolic health, and hormones like estrogen and parathyroid hormone. Insufficient remodeling may lead to residual.^{[11][2]}

III. FACTORS AFFECTING FRACTURE HEALING

Fracture healing is a complex biological process influenced by patient-related, fracture-related, and treatment-related factors. Any disturbance in these determinants can alter the normal healing cascade, resulting in delayed union or non-union.^[15]

3.1 Patient-Related Factors

Age plays a crucial role in fracture healing. Younger individuals heal faster due to rich vascularity and higher cellular activity, whereas elderly patients show delayed healing because of reduced osteogenic potential and associated comorbidities.^[16]

Nutritional status significantly affects bone repair. Adequate intake of protein, calcium, vitamin D, and micronutrients is essential for collagen synthesis and osteoblast function. Malnutrition has been strongly associated with delayed fracture healing.^[17]

Smoking adversely affects fracture repair by reducing tissue oxygenation and impairing osteoblast activity, leading to increased rates of non-union.^[18] Excessive alcohol consumption further disrupts bone metabolism and inflammatory responses during healing.^[19]

Systemic diseases such as diabetes mellitus delay fracture healing by impairing microcirculation and collagen synthesis, increasing susceptibility to infection and non-union.^[20] Osteoporosis compromises bone quality, increasing fixation failure and delayed union risk.^[21]

3.2 Fracture-Related Factors

Simple closed fractures heal faster due to preserved blood supply, while comminuted and open fractures demonstrate prolonged healing because of vascular disruption and soft tissue injury.^[22] Open fractures are particularly prone to infection, which further delays healing.^[23]

Adequate blood supply is essential for fracture repair, as angiogenesis supports nutrient delivery and osteoprogenitor cell migration. Compromised vascularity is a major cause of delayed union and non-union.^[24]

3.3 Treatment-Related Factors

Mechanical stability is fundamental to fracture healing. Both excessive rigidity and instability can negatively affect callus formation.^[25]

Certain medications influence bone repair. Prolonged use of NSAIDs inhibits prostaglandin synthesis and may delay fracture healing.^[26] While corticosteroids suppress osteoblast function and angiogenesis.^[27]

IV. COMPLICATIONS OF FRACTURE HEALING

Delayed union refers to slower-than-expected fracture healing without complete cessation of repair.^[28] Non-union occurs when the healing process stops entirely and is classified as hypertrophic or atrophic based on biological activity.^[29] Infection-related complications prolong inflammation and disrupt osteogenesis, often resulting in chronic non-union due to biofilm formation on implants.^[30] Implant failure further compromises stability and frequently necessitates revision surgery.^[31]

V. STRATEGIES TO ENHANCE FRACTURE HEALING

Fracture healing is a complex biological process influenced by local and systemic factors. In patients at high risk of delayed union or non-union—such as those with osteoporosis, diabetes, or polytrauma—strategies to enhance healing are essential. These strategies target mechanical stability, biological enhancement, and systemic optimization, combining pharmacological, surgical, and physical interventions.^[32]

5.1 Pharmacological Interventions

Pharmacological agents serve as adjuncts to conventional fracture care. Their primary goal is to stimulate osteogenesis, accelerate callus formation, and improve bone remodeling, particularly in fractures prone to delayed healing [33].

5.1.1 Growth Factors and Bone Morphogenetic Proteins (BMPs)

BMPs, especially BMP-2 and BMP-7, are critical regulators of osteoblast differentiation and bone matrix deposition. Clinical trials have shown that application of BMPs can significantly improve healing in complex fractures, including tibial non-unions and spinal fusions [34].

However, their routine use is limited due to high cost, risk of heterotopic ossification, inflammation, and potential for immunogenic reactions [35]. Careful patient selection and localized delivery methods are recommended to minimize complications.

5.1.2 Parathyroid Hormone (PTH) Analogues

Intermittent administration of PTH analogues, such as teriparatide, stimulates osteoblast activity and accelerates fracture repair. This approach has been particularly beneficial in osteoporotic fractures and delayed union cases, improving callus quality and reducing time to union [36]. Studies suggest that teriparatide may also reduce the incidence of implant failure in high-risk patients.

5.2 Surgical and Mechanical Interventions

Mechanical stability is a cornerstone of fracture healing. Surgical approaches aim to restore bone alignment, maintain stable fixation, and preserve periosteal blood supply, all of which are essential for biological repair [25].

5.2.1 Bone Grafts and Substitutes

Autologous bone grafts remain the gold standard for non-union management due to their osteogenic, osteoinductive, and osteoconductive properties [37]. However, harvesting autografts carries donor site morbidity, pain, and limited volume.

To overcome these limitations, allografts and synthetic substitutes (such as calcium phosphate ceramics) are increasingly used, offering structural support and promoting osteogenesis without the need for additional surgery [38].

5.2.2 Fixation Techniques

Modern fixation techniques, including locking plates, intramedullary nails, and minimally invasive devices, have improved outcomes in osteoporotic and comminuted fractures [39]. Achieving the optimal balance between stability and micro-motion is crucial: too rigid fixation can impede callus formation, whereas insufficient stability may cause implant failure [22].

5.2.3 External Fixation and Dynamization

External fixation is particularly useful for open fractures, polytrauma, and fractures with severe soft tissue injury. Controlled dynamization—gradual mechanical

loading through the fixator—stimulates cellular activity, enhances callus formation, and accelerates healing [40].

5.3 Physical Modalities

Adjunctive physical therapies can enhance biological repair by promoting cellular proliferation, angiogenesis, and matrix deposition.

5.3.1 Low-Intensity Pulsed Ultrasound (LIPUS)

LIPUS delivers mechanical energy to the fracture site, stimulating angiogenesis and osteogenic signaling pathways. Clinical trials have demonstrated reduced time to union in fresh fractures and non-union cases, particularly in tibial shaft fractures [41].

5.3.2 Electrical and Electromagnetic Stimulation

Electrical and electromagnetic stimulation techniques influence cellular calcium signaling, growth factor expression, and osteoblast differentiation. These therapies have shown benefits in delayed union and non-union, especially in patients who cannot undergo further surgery [42].

VI. SPECIAL CONSIDERATIONS

6.1 Pediatric Fracture Healing

Children generally heal faster than adults due to a highly active periosteum and abundant vascularity. However, fractures involving growth plates (physeal fractures) require careful management, as improper reduction can lead to growth arrest, angular deformity, or limb length discrepancy [43].

6.2 Osteoporotic Fractures

Osteoporotic fractures are associated with fragile bone, delayed healing, and higher rates of fixation failure. Optimized surgical techniques, combined with pharmacological support (e.g., bisphosphonates or PTH analogues), can improve healing outcomes and reduce complications [21].

6.3 Polytrauma and Comorbidity Effects

Patients with multiple injuries or systemic comorbidities (e.g., diabetes, chronic kidney disease, malnutrition) are at risk of delayed fracture healing due to metabolic stress, systemic inflammation, and impaired perfusion [44]. Early stabilization and multidisciplinary care are critical for favorable outcomes.

VII. CURRENT ADVANCES AND FUTURE PERSPECTIVES

Fracture healing research is increasingly focusing on biologically driven, personalized interventions. Innovations aim to enhance cellular activity, optimize scaffold design, and predict healing outcomes using advanced technology [32].

7.1 Tissue Engineering and Scaffolds

Biodegradable scaffolds provide structural support and facilitate cellular attachment, proliferation, and differentiation, mimicking the natural bone extracellular matrix. Scaffold-based therapies allow

localized delivery of growth factors, enhancing osteogenesis [41].

7.2 Stem Cell Therapy and Regenerative Medicine

Mesenchymal stem cells (MSCs) contribute to bone repair by differentiating into osteoblasts and secreting paracrine growth factors. Clinical studies in non-union fractures show accelerated healing and improved bone quality, with ongoing trials evaluating optimal cell sources, doses, and delivery methods [46].

7.3 Personalized Fracture Management (Imaging, AI)

Advances in imaging and artificial intelligence-based prediction models help clinicians forecast fracture healing outcomes, detect risk factors early, and guide individualized treatment plans [47]. This approach reduces complications and informs optimal fixation and pharmacotherapy strategies.

7.4 Nanotechnology in Bone Healing

Nanotechnology enables targeted drug delivery, enhanced biomaterial integration, and promotion of osteogenic signaling pathways. Nanostructured coatings and nanoparticles improve bone-implant integration and stimulate local bone regeneration [48].

VIII. CLINICAL IMPLICATIONS

A thorough understanding of fracture healing biology allows for early detection of complications and improved treatment planning.

8.1 Guidelines for Monitoring Fracture Healing

Regular clinical and radiological monitoring is essential to identify delayed union or non-union at an early stage. Parameters include pain assessment, functional status, radiographic bridging, and callus formation [49].

8.2 Early Detection of Complications

Complications such as infection, implant failure, malunion, or non-union should be identified early to prevent further morbidity and reduce the need for revision surgeries [30].

8.3 Multidisciplinary Approach

A multidisciplinary team—including orthopedic surgeons, pharmacists, physiotherapists, and nutritionists—enhances fracture healing, functional recovery, and patient adherence [44]. Interventions may include optimized nutrition, pharmacological support, and rehabilitation planning.

IX. CONCLUSION

Through the coordinated interaction of biological, mechanical, and systemic factors, fracture healing is a complex and dynamic regenerative process that restores the structural and functional integrity of bone. This process progresses through three well defined yet overlapping stages, namely inflammation, repair, and remodeling, all of which are essential for successful bone regeneration. Disruption at any stage, whether due to impaired vascularity, inadequate mechanical stability,

systemic disease, or unfavorable patient related factors, can delay healing and result in delayed union or non union. Advances in orthopedic care have been driven by an improved understanding of the cellular and molecular mechanisms underlying fracture repair, leading to the development of modern fixation techniques, biological augmentation strategies, and adjunctive therapies such as bone grafts, growth factors, and biophysical stimulation, which have enhanced healing outcomes, particularly in complex and high risk fractures. Despite these advances, complications remain a significant challenge, emphasizing the importance of individualized treatment planning and early identification of patients at risk for impaired healing. A comprehensive, evidence based approach that integrates surgical principles with biological optimization and patient specific considerations is therefore essential to improve fracture outcomes. Continued research in tissue engineering, regenerative medicine, and personalized orthopedic care holds promise for further enhancing fracture healing and reducing the burden of fracture related morbidity.

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